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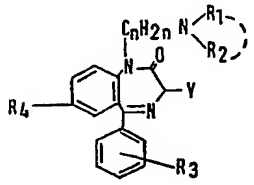
(72) Inventor JOHN LUNSDALE BETON

(54) BENZODIAZEPINES

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention is concerned with novel benzodiazepines e.g. 3 - substituted - 1 - alkylaminoalkyl - 1,4 - benzodiazepin - 2 - ones and more particularly with novel 3 - alkoxy and 3 - halo - 1 - alkylaminoalkyl - 5 - aryl - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - ones.

The invention provides compounds of Formula I:



I

wherein

R_1 is (lower)alkyl;

R_2 is (lower) alkyl or carbo(lower) alkoxy; or R_1 and R_2 may be concatenated to form a heterocyclic moiety selected from morpholino, pyrrolidinyl and piperidino;

R_3 is halogen or hydrogen;

R_4 is halogen, (lower) alkyl, cyano, trifluoromethyl, (lower)alkoxy, (lower)alkylmercapto or nitro;

Y is bromo, chloro, iodo or (lower)alkoxy;

n is an integer of from 2 to 8;

and the pharmaceutically acceptable acid addition salts and hydrates thereof.

In this specification the term "lower" when used in connection with an alkyl group or an alkoxyl group or with an alkyl portion of another group means that the alkyl group or portion contains up to 8 carbon atoms.

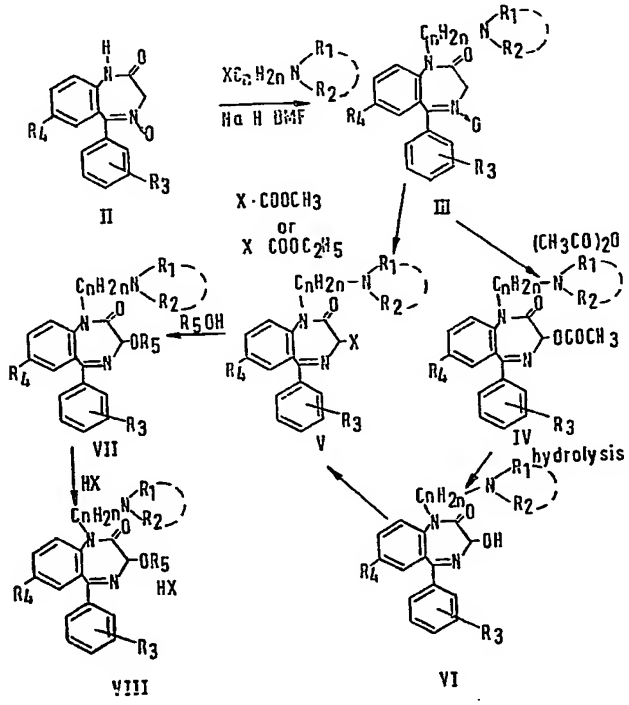
The benzodiazepines to which the invention relates may be prepared by the following processes which are included in the invention.

Thus a compound of the Formula I wherein Y is bromo, chloro or iodo may be prepared by reacting a corresponding N-oxide where Y is hydrogen with an alkyl haloformate. The resulting compound of formula I may then be converted into the corresponding 3-(lower) alkoxy compound by treatment with a lower alkanol.

The following reaction scheme illustrates this method of preparing the com-

[*Price 25p*]

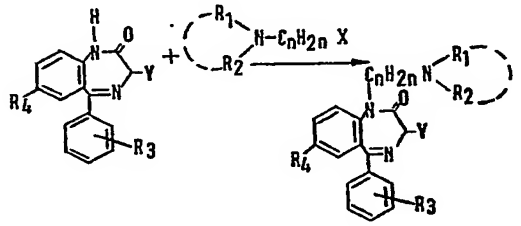
pounds of the invention including the preparation of the N-oxide starting material; and an alternative way of preparing the 3-halo compound:



wherein R_1, R_2, R_3, R_4 and n are the same as hereinabove described; R_5 is (lower)-alkyl and X is halogen.

The first process involves alkylating the appropriate 1,4 - benzodiazepin - 2 - one - 4 - oxide by a process similar to that described by Bell et al., J. Org. Chem., *27*, 562 (1962) and subsequently described by G. A. Archer et. al., U.S. Patent 3,299,053 (1967). Treatment of the N-oxide with an alkyl haloformate (e.g. methyl or ethyl chloroformate) affords the 3 - halo - 1,4 - benzodiazepin - 2 - one, which can be isolated as a solid or converted directly to the 3 - alkyl ether. Alternatively compound *V* can be obtained from compound *VI*. Compound *VI* is formed by treatment of compound *III* with acid anhydride to form the corresponding 3-acyloxy derivative *IV* followed by hydrolysis of the ester.

The following reaction scheme represents a second process for the preparation of compounds of the invention:



wherein R_1, R_2, R_3, R_4, n and X are the same as hereinabove described and Y is (lower)alkoxy. The above-described process involves the direct alkylation of the appropriately substituted 3 - alkoxy - 5 - aryl - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - ones with substituted aminoalkyl halides.

The direct alkylation is carried out in any inert, water miscible, organic solvent that is capable of dissolving the starting benzodiazepine at the operating temperature. Suitable examples include tetrahydrofuran, *p*-dioxane and 1,2-dimethoxyethane. The reaction may be carried out at about 0°C. to about 50°C. but it is preferred to run

the reaction at about 25°C. The reaction mixture is stirred for about 1 to about 24 hours and the mixture is then concentrated. The product is then extracted with water and ether and purified by conventional methods.

Compounds of the invention have been tested by orally administering to three mice (CF-1 14 to 24 grams) at each of the following doses 400, 127, 40, 12.7 and 4 mg./kg.

The animals are watched for a minimum of two hours during which time signs of general stimulation (i.e. increased spontaneous motor activity, hyperactivity on tactile stimulation, twitching), general depression autonomic activity (i.e. miosis, mydriasis, diarrhea) are noted, The animals are tested for changes in reflexes (i.e. flexor, extensor) and are rated by use of a pole climb and inclined screen for the presence of sedation ataxia. The "Eddy Hot-Plate Method", (Nathan B. Eddy and Dorothy Leimbach, J. Pharmacol. Exper. Therap. *107*: 385, 1953) is used to test for analgesia. The experiment is terminated by subjecting each animal to a maximal electroshock to test for anticonvulsant activity.

The compounds of the invention are pharmacologically active as anticonvulsants when orally administered to mammals at a dosage of from 4 milligrams to 400 milligrams per kilogram of body weight.

Thus the invention also provides pharmaceutical compositions comprising a compound of the invention in association with a pharmaceutically acceptable carrier. Such composition can be in any of the usual oral or parenteral formulations which can be liquids or solids or mixtures thereof, for example ampoules, vials, powders, tablets, capsules, sterile solutions, suspensions, suppositories, troches, emulsions, syrups and elixirs. It can also be in unit dose form and the quantity of active ingredient therein can be from 1 mg. or less to 500 mg. or more according to the particular need and activity of the active ingredient.

The following examples are set forth to illustrate but not to limit the scope of the invention. Examples 1, 2, 5 and 9 are reference Examples illustrating the preparation of starting materials.

EXAMPLE 1

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide

To a slurry of sodium hydride (2.6 g. of 50% sodium hydride suspension previously washed with pentane) in 60 ml of dimethylformamide was added over a five minute period a solution of 12.84 g. of 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide in 20 ml of dimethylformamide. The colour of the solution varied during the addition from a light yellow to a deep red and remained yellow. A toluene solution of diethylaminoethyl chloride (prepared by neutralizing 7.34 g. of diethylaminoethyl chloride hydrochloride with 80 ml of 4*N* sodium hydroxide, extracting with a total of 80 ml of toluene, and, drying over anhydrous sodium carbonate) was added over 20 min. to the reaction with stirring. The mixture was stirred for 16 hr. at 30°. The solvent was evaporated in vacuo and the residue slurried in water and extracted first with methylene chloride and then with ethyl acetate. The methylene chloride extract was extracted with several portions of 2*N* hydrochloric acid and the combined acid extracts were neutralised with sodium bicarbonate and re-extracted into methylene chloride. The methylene chloride soln. was dried over anhydrous magnesium sulfate and evaporated in vacuo to give 2.70 g. of the title compound, m.p. 164—166°. Additional product was obtained from the ethyl acetate extract by extraction into 2N hydrochloric acid. Neutralisation with sodium bicarbonate caused a light tan solid to separate from the reaction mixture. Filtration of the solid and recrystallisation from boiling ethanol gave additional 7.10 g. of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide, m.p. 164—166°; nmr ($CDCl_3$) δ 1.0 (t, 6, J=7Hz), 2.62 (m, 6), 4.05 (m, 2), 4.67 (s, 2), 6.95 (d, 1, J=2Hz) and 7.23—7.86 (m, 6).

Anal. Calcd. for $C_{21}H_{23}N_3O_2Cl_2$: C, 60.00; H, 5.51; N, 10.00.
Found: C, 59.86; H, 5.66; N, 10.00.

EXAMPLE 2

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide

To a chilled slurry of sodium hydride [15.6 g. (0.325 mole) of 50% oil dispersion washed several times with pentane] in 360 ml. of dimethylformamide was

added dropwise over 20 min. a solution of 77 g. (0.24 mole) of 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide in 120 ml. of dimethylformamide. The mixture was stirred for 1 hr. at 5—10° and was treated dropwise with a toluene solution of *β* - diethylaminoethyl chloride. [The toluene solution was prepared by neutralising 44.4 g. (0.275 mole) of *β* - diethylaminoethyl chloride with 120 ml of 4*N* sodium hydroxide, extracting 3 times with 160 ml portions of toluene and drying the toluene extracts over anhydrous sodium carbonate]. After the reaction mixture was stirred at 27° for 18 hrs. The dimethylformamide was evaporated on a rotary evaporator at ~35—40°. The residue was slurried with 200 ml of water, filtered, and dried to give 85.0 g. of crude product. Recrystallisation by dissolving the solid in 850 ml of boiling ethanol and concentrating to 650 ml gave 51.0 g. of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide, m.p. 166—168°. This was identical in every respect with the material obtained by Example *1*.

EXAMPLE 3

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one

To 180 ml of ethyl chloroformate was added portionwise 30 g. (0.0715 mole) of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide with stirring and gradual warming. A vigorous evolution of gas occurred and the temperature was increased to cause gentle refluxing. After 2 hrs. most of the solvent evaporated and additional 180 ml of ethyl chloroformate was added and refluxed for one hour. The excess ethyl chloroformate was evaporated *in vacuo* and residual traces were removed by codistillation with three portions of toluene. The residue was dissolved in 240 ml of methanol and refluxed for 1.5 hr. and allowed to stand for 16hr. at 27°. After evaporation of the solvent the residue was dissolved in benzene and extracted with four 40 ml. portions of 6*N* hydrochloric acid. The combined acid extracts were washed with benzene and neutralised with 95 g. of 50% sodium hydroxide solution. The oily mixture was extracted with three portions of benzene and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the benzene *in vacuo* gave an oil which on treatment with 100 ml of cyclohexane afforded 10.8 g. of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one, m.p. 123—125°; nmr ($CDCl_3$) δ 1.0 (t, 6, J=7Hz), 2.56 (q, 6, J=7Hz), 3.64 (s, 3), 4.03 (q, 2, J=7Hz), 4.70 (s, 1), 7.03 (d, 1, J=25 Hz), and 7.75 to 7.78 (m, 6).

Anal. Calcd for $C_{22}H_{25}Cl_2N_3O_2$: C, 60.83; H, 5.80; N, 9.67
Found: C, 60.94; H, 5.97; N, 9.62.

EXAMPLE 4

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one, hydrochloride hydrate

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 3 - one (9.00 g.) was dissolved in 270 ml of water containing 20.70 ml of 1*N* hydrochloric acid. The solution was lyophilized to dryness to give 9.8 g. of product, shrinks on melting at 90° and coalesces as a liquid at 122°, nmr ($CDCl_3$) δ 1.42 (t, 6, J=7Hz), 3.25 (m, 6), 3.65 (s, 3), 4.67 multiplet with a singlet superimposed at 4.75 total of 3, 7.06 (d, 1, J=2, 5Hz), and 7.37 to 7.9 (m, 6).

Anal. Calcd for $C_{22}H_{26}N_3Cl_3O_2 . H_2O$:
C, 54.05; H, 5.77; N, 8.60; Cl, 21.76; H_2O, 3.82.
Found:
C, 54.18; H, 5.39; N, 8.57; Cl, 22.43; H_2O, 3.36.

EXAMPLE 5

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide

An ice-cold solution of 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide (12.84 g., 0.04 moles) in 20 ml of anhydrous dimethylformamide was added to an ice-cold mixture of pentane washed sodium

hydride (2.6 g., 0.54 mole) and dimethylformamide (20 ml). A solution of 2 - dimethylaminoethyl chloride (from 6.5 g., 0.045 mole of 2 - dimethylaminoethyl chloride hydrochloride) in 50 ml of toluene was added to the yellow reaction solution. The reaction was stirred for 21 hours at room temperature and flash evaporated. The residue was dissolved in dichloromethane and was extracted with 500 ml of 2N hydrochloric acid. The aqueous phase was separated, made basic with sodium carbonate, and extracted with ethyl acetate. Evaporation of the organic phase after drying left a viscous gum (6 g.) which was chromatographed on 90 g. of silica gel. The column was eluted with solvents ranging from 3:1 ether-pentane to 3:1 ether acetone, a total of seventy 100 ml. fractions were collected. The combined residues of fractions 45 through 67 gave a yellow oil which crystallised from ether-pentane. The crystalline product (3.1 g. 17.5% yield) had a m.p. of 152—153.5°; nmr (δ) 2, 2 (s, 6), 2.52 (t, 2), 4.0 (t, 2), 4.68 (s, 2), 6.95 (d, 1), 7.4 (m, 6).

Anal. Calcd for $C_{19}H_{19}Cl_2N_3O_2$: C, 58.17; H, 4.88; N, 10.71
Found: C, 58.20; H, 4.81; N 10.68.

EXAMPLE 6

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one, 2 - [7 - Chloro - 5 - (*o* - chlorophenyl) - 2,3 - dihydro - 3 - methoxy - 2 - oxo - 1*H* - 1,4 - benzodiazepin - 1 - yl]ethyl methylcarbamic Acid Ethyl Ester and 5 - (*o* - chlorophenyl - 3,7 - dichloro - 1 - (2 - dimethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one

Method I

A mixture of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one 4 - oxide (2 g., 5.1 mmoles) and 60 ml of ethyl chloroformate was refluxed for 0.5 hr. Addition of 60 ml of methyl chloroformate and further reflux caused the solid to go into solution. Refluxing was continued for 40 min., after which the excess chloroformates were flash evaporated. The residual gum dissolved in 50 ml. of anhydrous methyl alcohol was refluxed for 40 min. The solvent was evaporated, and the residue dissolved in benzene was extracted with a total 150 ml of 6*N* - hydrochloric acid. The aqueous phase was made basic with sodium carbonate and extracted with benzene. Evaporation of the benzene gave a gummy residue which was then chromatographed on 40 g. of silica gel using ether-acetone (9:1) as eluant. Forty 100 ml fractions were collected. Evaporation of fraction 3 and 4 gave an oil which was crystallised from ether pentane to give 370 mg (15.5% yield) of solid [2 - [7 - chloro - 5 - (*o* - chlorophenyl) - 2,3 - dihydro - 3 - methoxy - 2 - oxo - 1*H* - 1,4 - benzodiazepin - 1 - yl]ethyl]methylcarbamic acid, ethyl ester, m.p. 119—121°, nmr δ 1.27 (t, 3), 3.0 (s, 3), 3.5 (m, 2), 3.65 (s, 3), 4.1 (two superimposed triplets, 4), 4.72 (s, 1), 7.08 (m, 1), 7.5 (m, 6).

Anal. Calcd for $C_{22}H_{23}N_3Cl_2O_4$: C, 56.90; H, 4.99; N, 9.05.
Found: C, 56.72; H, 4.96; N, 9.08.

The residue of fraction 9 gave 50 mg. (2.4% yield) of 5 - (*o* - chlorophenyl) - 3,7 - dichloro - 1 - (2 - dimethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one, m.p. 158—160° (from ether pentane); nmr δ 2.28 (s, 6), 2.6 (t, 2), 4.1 (m, 2), 5.01 (s, 1), 7.1 (m, 1), 7.4 (m, 6).

Anal. Calcd for $C_{19}H_{16}Cl_3N_3O$: C, 55.56; H, 4.42; N, 10.23.
Found: C, 55.74; H, 4.72; N, 10.39.

The residue of fractions 15—33 gave 500 mg (24% yield) of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one, m.p. 136—137° (from ether pentane), nmr δ 2.22 (s, 6), 2.53 (t, 2), 3.66 (s, 3), 4.1 (m, 2), 4.71 (s, 1), 7.1 (m, 1), 7.5 (m, 6).

Anal. calcd for $C_{20}H_{21}Cl_2N_3O_2$: C, 59.12; H, 5.21; N, 10.34
Found: C, 58.70; H, 5.14; N, 10.22.

EXAMPLE 7

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one from 7 - Chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one

Method II

To a mixture of pentane-washed sodium hydride (0.5 g., 0.01 moles) and 25 ml of anhydrous tetrahydrofuran a solution of 3.34 g. (0.01 moles) of 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one was added. To the yellow reaction solution was added a solution of 2 - dimethylaminoethyl chloride (from 1.4 g., 0.01 moles of 2 - dimethylaminoethyl chloride hydrochloride, neutralised with pentane-washed sodium hydride, 0.5 g., 0.01 moles) in 25 ml of anhydrous dimethylformamide. The mixture was stirred for 18 hours at room temperature. After flash evaporation of the solvent the residue was extracted with dichloromethane and 100 ml of 3N hydrochloric acid. The aqueous phase was separated, made basic with sodium carbonate and extracted with dichloromethane. The organic extract was dried and evaporated to give 2.5 g. of a gum. The gum was chromatographed on 50 g. of silica gel, eluted with 9:1 ether-acetone. A total of 34 fractions were collected. The desired product, 300 mg (7.5% yield) was obtained from the residue of fractions 15—33 by recrystallisation from ether, pentane. The m.p., ir and nmr spectra were identical to those described above in Method I in Example 6 for 7 - chloro - 1 - (2 - dimethylaminoethyl) - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one.

EXAMPLE 8

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (3 - dimethylaminopropyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one hydrochloride hydrate

The procedure was essentially the same as the one described above in Example 5, using 3 - dimethylaminopropyl chloride and 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one - 4 - oxide. The same molar quantities of reagents were used. In this case the intermediate N-oxide was isolated as a gum but was not purified, nmr δ 2.2 (s, 6), 2.4—4.2 (m, 6), 4.7 (s, 2), 7 (m, 1), 7.4 (m, 6).

After treating the N-oxide residue with methyl chloroformate (instead of ethyl chloroformate) (as described above in Example 6 Method I) and employing a similar work up procedure the residue obtained was dissolved in ether instead of being purified by chromatography. Addition of a saturated solution of hydrogen chloride gas in ether precipitated a solid which was scratched and washed repeatedly with ether. A solid (3 g., 16% yield) was obtained after drying which did not melt but foamed between 115° and 130°, nmr δ 1.7—2.7 (m, 4), 2.2 (s, 6), 3.63 (s, 3), 3.7—4.4 (m, 2), 4.71 (s, 1), 7 (m, 1), 7.5 (m, 6).

Anal. Calcd for $C_{21}H_{20}Cl_2N_3O_3$: C, 53.12; H, 5.52; N, 8.85.
Found: C, 52.82; H, 5.18; N, 8.83.

EXAMPLE 9

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - hydroxy - 2*H* - 1,4 - benzodiazepin - 2 - one, acetate

A slurry of 6.00 g (0.014 mole) of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one - 4 - oxide in 60 ml of acetic anhydride was heated with stirring at 95° for 3 hr. The acetic anhydride was evaporated in vacuo and the residue was dissolved in ether and allowed to stand to allow 1.2 g. of unreacted starting material to crystallise. The supernatant liquid was decanted and concentrated on a rotary evaporator to an oil. Treatment with 50% aqueous ethanol afforded 2.28 g. of crystalline product, which was recrystallised from methylene chloridehexane to give 2.16 g. of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - hydroxy - 2*H* - 1,4 - benzodiazepin - 2 - one, acetate, m.p. 144—146°; nmr ($CDCl_3$) δ 1.0 (6, t, J=7Hz), 2.29 (s, 3), 2.57 (q, 6, J=7Hz), 4.0 (m, 2), 5.91 (s, 1), 7.03 (d, 1, J=2.5Hz) and 7.25—7.85 (m, 6).

Anal. Calcd for $C_{23}H_{25}N_3O_3Cl_2$: C, 59.75; H, 5.45; N, 9.09.
Found: C, 59.75; H, 5.43; N, 9.03.

EXAMPLE 10

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 4,5 - dihydro - 2*H* - 1,4 - benzodiazepin - 2,3 - (1*H*) - dione hemihydrate, and 7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - hydroxy - 2*H* - 1,4 - benzodiazepin - 2 - one

To a solution of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - hydroxy - 2*H* - 1,4 - benzodiazepin - 2 - one, acetate, (2.4 g., 5.2 mmoles) in 25 ml of 95% ethyl alcohol was added 1.3 ml (5.2 mmoles) of 4N sodium hydroxide. The solution was stirred for one hour at room temperature, acidified with glacial acetic acid, and extracted with dichloromethane-water. The organic phase was separated, dried and flash evaporated. The oily residue was dissolved in 20 ml. of dichloromethane, to which 60 ml of pentane was added. A solid material crystallised out of solution after the flask was scratched. Filtration gave a white solid, m.p. 169—172°.

After the product was dried at 70° in a vacuum oven for two hours the m.p. changed to 157—159°. A total of 1.4 g. (3.27 mmoles, 62% yield) of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - q(2 - diethylaminoethyl) - 4,5 - dihydro - 2*H* - 1,4 - benzodiazepin - 2,3 - (1*H*) - dione, hemihydrate was obtained; nmr δ 0.95 (t, 6), 2.3—3 (m, 6), 3.5—4.7 (m, 2), 6.2 (s, 1), 6.52 (d, 1), 7.2—7.7 (m, 6).

Anal. Calcd for $C_{21}H_{23}Cl_2N_3O_2 . 1H_2O$: C, 58.80; H, 5.33; N, 9.85
Found: C, 58.75; H, 5.77; N, 9.79

From the mother liquor of the above product a second crop of crystals separated overnight. Recrystallisation from ether-pentane gave 0.27 (0.64 mmole, 12% yield) of 7 - chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - hydroxy - 2*H* - 1,4 - benzodiazepin - 2 - one, m.p. 138—140°; nmr δ 0.98 (t, 6), 2.3—3.9-(m, 6), 3.9—4.5 (m, 2), 4.98 (s, 1), 7.05 (d, 1), 7.3—7.8 (m, 6).

Anal. Calcd for $C_{21}H_{23}Cl_2N_3O_2$: C, 60.04; H, 5.51; N, 9.99
Found: C, 59.88; H, 5.45; N, 10.07.

The latter product can be converted to the corresponding 3 - chloro compound by standard methods.

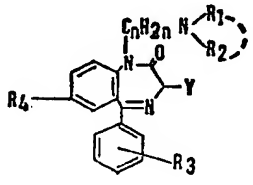
EXAMPLE 11

7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one

To a solution of 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one (3.55 g., 0.01 mole) in 100 ml of tetrahydrofuran was added sodium iodide (3 g., 0.02 mole) in 5 ml of water, diethylaminoethyl chloride hydrochloride (1.7 g., 0.01 mol) in 5 ml of water and potassium hydroxide (1.3 g., 0.023 mole) in 5 ml of water. The solution was stirred at room temperature for 18 hours and was then concentrated by flash evaporation. The residue was extracted with water and ether. The organic phase was separated, dried over anhydrous magnesium sulfate and evaporated to give a solid residue (3.27 g.), which was recrystallised from cyclohexane and ether. Four crops of crystals were obtained, the first, third and fourth gave a total 2.7 g. (1.6 g., 0.7 g. and 0.44 g. respectively) of product m.p. 122—125°. The crystalline material obtained from the second crop (0.25 g.) was the starting material, the conversion yield amounted to 68.3%.

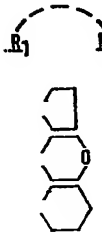
EXAMPLE 12

By procedures analogous to those employed above the following compounds are prepared:



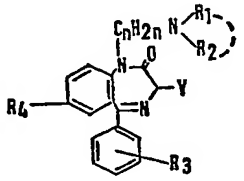
I

R_1	R_2	R_3	R_4	Y	n
$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	4-F	Cl	Br	2
CH_3	CH_3	4-Cl	Br	OC_2H_5	6
C_2H_5	C_2H_5	2-Br	CH_3	OC_3H_7	8
CH_3	CH_3	4-I	C_2H_5	OC_4H_9	5
C_2H_5	C_2H_5	4-Cl	OCH_3	I	4
CH_3	$CO_2C_3H_7$	H	OC_2H_5	OCH_3	3
CH_3	$CO_2C_4H_9$	2-Cl	F	OCH_3	2
C_2H_5	C_2H_5	2-F	SCH_3	OCH_3	2
C_2H_5	C_2H_5	H	NO_2	OCH_3	2
CH_3	CH_3	2-F	CN	OCH_3	2
CH_3	CH_3	4-Cl	SC_2H_5	OCH_3	2

	R_3	R_4	Y	n
	4-Cl	$n\text{-}C_3H_7$	Cl	2
	4-Br	$-OC_3H_7$	OCH_3	2
	2-Br	$-C_2H_5$	OCH_3	2

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein R_{11} is (lower)alkyl; R_2 is (lower)alkyl or carbo (lower) alkoxy; or R_1 and R_2 may be concatenated to form (together with the nitrogen atom to which they are attached) a heterocyclic moiety selected from morpholino, pyrrolidinyl and piperidino; R_3 is halogen or hydrogen; R_4 is halogen, (lower)alkyl, cyano, trifluoromethyl, (lower)alkylmercapto or nitro; Y is bromo, chloro, iodo or (lower) alkoxy; n is an integer of from 2 to 8; and the pharmaceutically acceptable acid addition salts and hydrates thereof.

2. A modification of the compound claimed in Claim 1, wherein R_4 is a lower alkoxy group.

3. A compound as claimed in Claim 1, wherein R_3 and R_4 are each chlorine and R_3 is in the ortho position.

4. A compound as claimed in Claim 1 or Claim 3 wherein R_1 is methyl.

5. A compound as claimed in Claim 1, Claim 3 or Claim 4, wherein R_2 is methyl.

6. A compound as claimed in Claim 1 or Claim 3, wherein R_1 and R_2 are each ethyl.

7. A compound as claimed in any one of Claims 1, or 3 to 6 wherein n is 2 or 3.

8. 7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one and the pharmaceutically acceptable acid addition salts and hydrates thereof.

9. 7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - diethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one hydrochloride hydrate.

10. 7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one and the pharmaceutically acceptable acid addition salts and hydrates thereof.

11. 7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (3 - dimethylaminopropyl) - 1,3 -

dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one, and the pharmaceutically acceptable acid addition salts and hydrates thereof.

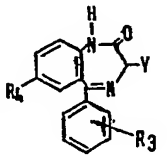
12. 7 - Chloro - 5 - (*o* - chlorophenyl) - 1 - (3 - dimethylaminopropyl) - 1,3 - dihydro - 3 - methoxy - 2*H* - 1,4 - benzodiazepin - 2 - one hydrochloride hydrate.

13. 2 - [7 - Chloro - 5 - (*o* - chlorophenyl) - 2,3 - dihydro - 3 - methoxy - 2 - oxo - 1*H* - 1,4 - benzodiazepin - 1 - yl]ethyl methylcarbamic acid ethyl ester.

14. A novel benzodiazepine as claimed in claim 1 or 2, substantially as hereinbefore described with reference to any one of Examples 3, 4, 6, 7, 10, 11 or 12.

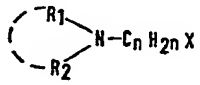
15. A novel benzodiazepine as claimed in claim 1, substantially as hereinbefore described with reference to Example 8.

16. A process for the preparation of a compound as claimed in Claim 1, wherein Y is lower alkoxy, which process comprises contacting a compound of the formula



(IX)

wherein R_3 and R_4 are as defined in Claim 1 and Y is lower alkoxy with a compound of the formula



wherein R_1 and R_2 are as defined in Claim 1 and X is halogen, in the presence of an inert, water miscible, organic solvent at a temperature of about 0°C to about 50°C and recovering the product.

17. A process as claimed in Claim 16, wherein the compound prepared is a compound as claimed in any one of claims 3 to 12.

18. A process according to Claim 16 or Claim 17 wherein the reaction is carried out at about 25°C.

19. A modification of the process claimed in Claim 16, wherein the starting material of formula IX is one in which R_4 is alkoxy and the product is one as claimed in Claim 2.

20. A process for preparing a compound as claimed in Claim 1, wherein Y is a lower alkoxy group which process comprises treating a corresponding compound in which Y is bromo, chloro or iodo with a lower alkanol.

21. A modification of the process claimed in Claim 20 wherein the starting compound is one in which R_4 is lower alkoxy and the product is one as claimed in Claim 2.

22. A process as claimed in Claim 16, substantially as hereinbefore described with reference to Example 7 or 11.

23. A process as claimed in Claim 20, substantially as hereinbefore described with reference to Example 3 or Example 6.

24. A process as claimed in Claim 20, substantially as hereinbefore described with reference to Example 8.

25. A novel benzodiazepine whenever prepared by a process as claimed in any one of Claims 16—18, 20, 22 or 23.

26. A novel benzodiazepine whenever prepared by a process as claimed in any one of Claims 19, 21 or 24.

27. A process for preparing a compound as claimed in Claim 1, wherein Y is bromo, chloro or iodo which process comprises reacting a corresponding N-oxide, where Y is hydrogen with an alkylhaloformate.

28. A process as claimed in Claim 27 wherein the alkyl haloformate is methyl or ethyl chloroformate.

29. A process as claimed in Claim 27 substantially as hereinbefore described with reference to Example 3 or 6.

30. A modification of the process claimed in Claim 27 or 28 wherein in the N-oxide starting material R_4 is (lower) alkoxy and a compound as claimed in Claim 2 is obtained.

31. A novel benzodiazepine whenever prepared by a process as claimed in any one of Claims 27, 29 or 30.

32. A novel benzodiazepine whenever prepared by a process as claimed in Claim 28.

33. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1, or 3 to 14 and a pharmaceutically acceptable carrier.

34. A pharmaceutical composition comprising a compound as claimed in Claim 2 or 15 and a pharmaceutically acceptable carrier.

G. R. PORTER,
Chartered Patent Agent.

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